(10)

PATENT SPECIFICATION (11) 1 598 628

1 598 628

(21) Application No. 23611/78 (22) Filed 26 May 1978
(31) Convention Application No. 803009
(32) Filed 3 June 1977
(31) Convention Application No. 826796
(32) Filed 22 Aug. 1977
(31) Convention Application No. 848959
(32) Filed 7 Nov. 1977 in
(33) United States of America (US)
(44) Complete Specification published 23 Sept. 1981
(51) INT CL³ C07D 233/64 A61K 31/415
(52) Index at acceptance
C2C 1410 202 215 246 247 250 252 25Y 30Y 320 326 373 37Y 703 747 758 802 80Y AA RH

(19)



(54) GUANIDINE DERIVATIVES

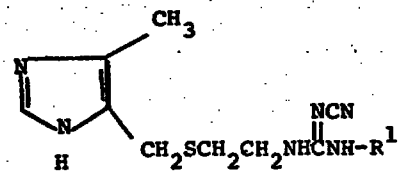
(71) We, BRISTOL-MYERS COMPANY, a Corporation organised and existing under the laws of the State of Delaware, United States of America, of 345 Park Avenue, State of New York, 10022, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to certain N - cyano - N′ - {2 - [(4 - methyl - 5 - imidazolyl)methylthio]ethyl} - N″ - alkynylguanidines which are H_2 receptor blocking agents, which inhibit gastric acid secretion and which are useful in the treatment of ulcers.

The clinical objective in treatment of peptic ulcer disease is to decrease gastric acid secretion, based on the principle "no acid, no ulcer". Traditional peptic ulcer disease therapy involves control of diet and the use of antacids and anticholinergics.

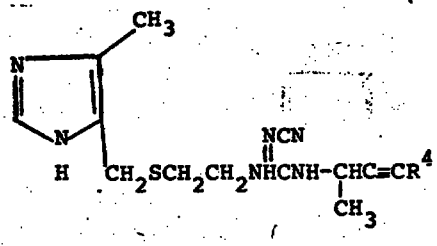
There is evidence indicating that histamine may be the final common pathway for stimulation of gastric secretion. This effect of histamine is mediated via H_2 receptors and is not inhibited by the classical antihistamines, which are H_1 receptor blockers. A number of specific H_2 receptor blocking agents (H_2 receptor antagonists) are now known. These compounds inhibit basal acid secretion, as well as secretion by other known gastric acid stimulants, and are useful in the treatment of peptic ulcers.

Accordingly, the present invention provides histamine H_2 receptor antagonists which are effective inhibitors of gastric secretion in animals, including man, which are useful in the treatment of peptic ulcer disease, and which have the formula



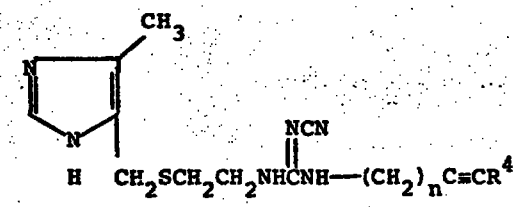
wherein R^1 is a straight or branched chain alkynyl group containing from 3 to 9 carbon atoms, inclusive, and non-toxic pharmaceutically acceptable acid addition salts thereof.

A preferred embodiment of the invention is a compound of the formula



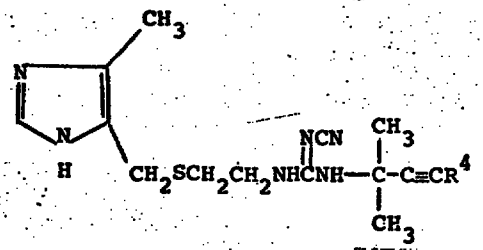
wherein R^4 is hydrogen or methyl, or a non-toxic pharmaceutically acceptable acid addition salt thereof.

Another preferred embodiment of the invention is a compound of the formula



wherein R^4 is hydrogen or methyl and *n* is an integer of from 1 to 6, inclusive, or a nontoxic pharmaceutically acceptable acid addition salt thereof. Preferably *n* is 1 or 2 in these compounds.

Another preferred embodiment of the invention is a compound of the formula



wherein R^4 is hydrogen or methyl, or a nontoxic pharmaceutically acceptable acid addition salt thereof.

A more preferred embodiment of the invention is N - cyano - N′ - [2 - [(4 - methyl - 5 - imidazolyl)methylthio]ethyl] - N″ - (2 - butyn - 1 - yl)guanidine or a nontoxic pharmaceutically acceptable acid addition salt thereof.

Another more preferred embodiment of the invention is N - cyano - N′ - [2 - [(4 - methyl - 5 - imidazolyl)methylthio]ethyl] - N″ - (3 - butyn - 1 - yl)guanidine or a nontoxic pharmaceutically acceptable salt thereof.

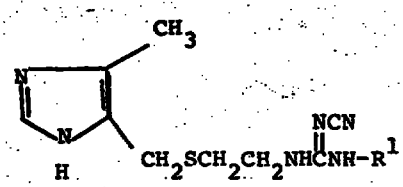
Another more preferred embodiment of the invention is N - cyano - N′ - [2 - [(4 - methyl - 5 - imidazolyl)methylthio]ethyl] - N″ - (4 - pentyn - 1 - yl)guanidine or a nontoxic pharmaceutically acceptable acid addition salt thereof.

Another more preferred embodiment of the invention is N - cyano - N′ - [2 - [(4 - methyl - 5 - imidazolyl)methylthio]ethyl] - N″ - (2 - methyl - 3 - butyn - 2 - yl)guanidine or a nontoxic pharmaceutically acceptable acid addition salt thereof.

Another more preferred embodiment of the invention is N - cyano - N′ - [2 - [(4 - methyl - 5 - imidazolyl)methylthio]ethyl] - N″ - (3 - butyn - 2 - yl)guanidine or a nontoxic pharmaceutially acceptable acid addition salt thereof.

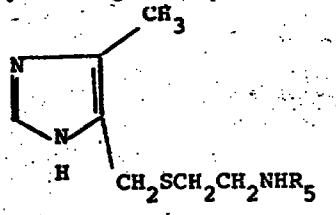
The most preferred embodiment of the invention is N - cyano - N′ - [2 - [(4 - methyl - 5 - imidazolyl)methylthio]ethyl] - N″ - propargyl - guanidine or a nontoxic pharmaceutically acceptable acid addition salt thereof.

The present invention also provides for the preparation of a compound of the formula



I

wherein R^1 is a straight or branched chain alkynyl group containing from 3 to 9 carbon atoms, inclusive, or a non-toxic pharmaceutically acceptable acid addition salt thereof characterized by reacting a compound of the formula

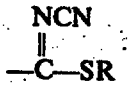


II

or an acid addition salt thereof with a compound of the formula

$$R_6NHR^1 \qquad \text{III}$$

wherein R^1 is as defined above and one of R_5 and R_6 is H and the other is the group

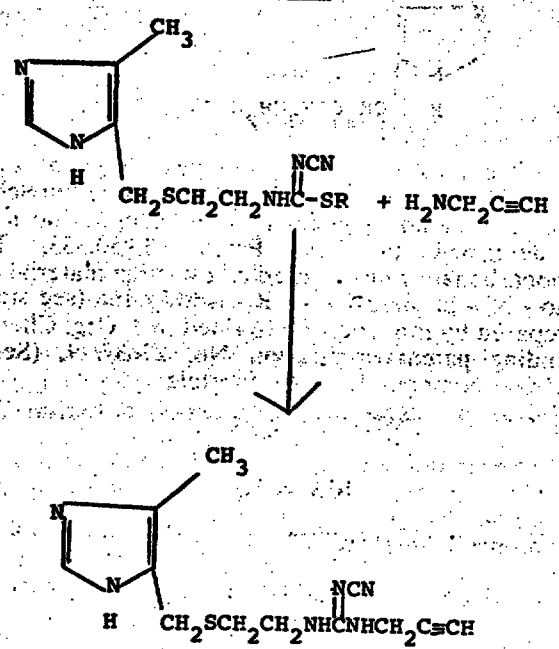


where —SR is a leaving group, and, if desired, converting the resulting compound of formula I in basic form or an acid addition salt thereof to the corresponding non-toxic pharmaceutically acceptable acid addition salt or free base form.

The reaction is conducted in a non-reactive solvent at a temperature above ambient temperature. In a preferred embodiment equimolar quantities of the compounds of formulae II and III are used.

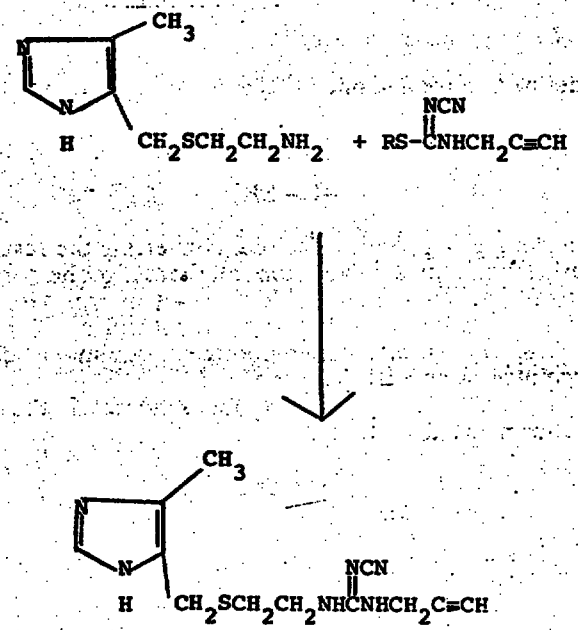
This process is illustrated by the reaction schemes I and II below for a preferred compound of the invention.

Scheme I



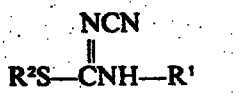
The reaction is conducted in a non-reactive solvent at a temperature above room temperature. As will be appreciated by those skilled in the art, R may be any substituent such that —SR will be a leaving group. Thus, R may be (lower)alkyl, aryl, substituted aryl (e.g. *p* - nitrophenyl), aralkyl, —CH_2CN, —CH_2COOH, or —CH_2COOR', where R' is a C_{1-9} alkyl group. The N - cyano - N' - [2 - [(4 - methyl - 5 - imidazolyl)methylthio]ethyl] - S - R - isothiourea starting materials may be prepared by the procedures described in Belgian Patent 804,144. The alkynylamine starting materials are either commercially available or may be prepared by methods described in Bull. Soc. Chim. Fr., 490 (1958), Bull. Soc. Chim. Fr., 592 (1967) and Annales de Chimie (Paris), *3*, 656 (1958).

Scheme II



The reaction is conducted in a non-reactive solvent at a temperature above room temperature. The substituent R may be as indicated in Scheme I, above. The 2 - [(4 - methyl - 5 - imidazolyl)methylthio]ethylamine starting material may be prepared as described in U.S. Patent 3,950,353. The disubstituted cyanodithioiminocarbonate which is used as a starting material for the preparation of the N - cyano - N' - propargyl - S - R - isothiourea (see step a of Example 2) may itself be prepared by procedures described in J. Org. Chem., *32*, 1566 (1967).

Our co-pending patent application No. 27637/79, (Serial No. 1598629) describes and claims compounds of the formula



wherein R^1 is as above defined and R^2 is C_{1-9} alkyl, aryl, substituted aryl, aralkyl,

$$-CH_2CN, \quad -CH_2COOH \text{ or } -CH_2COOR^1$$

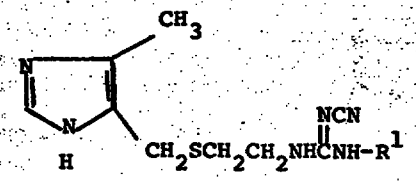
wherein R^1 is C_{1-9} lower alkyl.

It has additionally been discovered that in the preparation of N - cyano - N' - [2 - [(4 - methyl - 5 - imidazolyl)methylthio]ethyl] - N" - propargylguanidine via Reaction Scheme I, selected reaction conditions thereof give greatly improved yields of product as well as a product containing less impurities. The latter condition has the added advantage of permitting the initial ("crude") product to be isolated as a crystalline solid which may be more highly purified by simple recrystallization, and avoids the chromatographic purification of the initial crude product which we previously considered desirable when using other reaction conditions.

The selected reaction conditions referred to above consist of using methanol as solvent, utilizing a more concentrated solution in the reaction (approximately 1 gram of the substituted isothiourea per 5 ml of methanol), the use of a nitrogen sweep of the reaction apparatus during the reaction, and the utilization of freshly distilled propargylamine in the reaction.

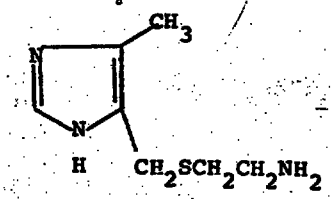
Experiments have shown that the use of a nitrogen sweep during the reaction avoids the formation of small amounts of two as yet unidentified by-products which are formed in the absence of a nitrogen sweep. These by-products, when present, resisted removal by column chromatography and recrystallization. It is believed that the nitrogen sweep prevents the formation of these by-products by removing the methyl mercaptan gas as quickly as it is formed.

The present invention also provides the process for production of a compound having the structure



I

wherein R^1 is a straight or branched chain alkynyl group containing from 3 to 9 carbon atoms, inclusive or a non-toxic pharmaceutically acceptable acid addition salt thereof which comprises reacting a compound of the formula

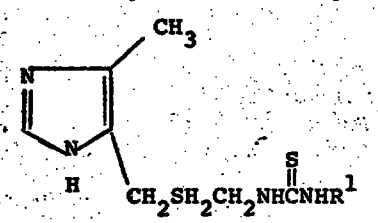


V

with a compound of the formula

$$S=C=NR^1$$

wherein R^1 is as defined above, to produce the compound

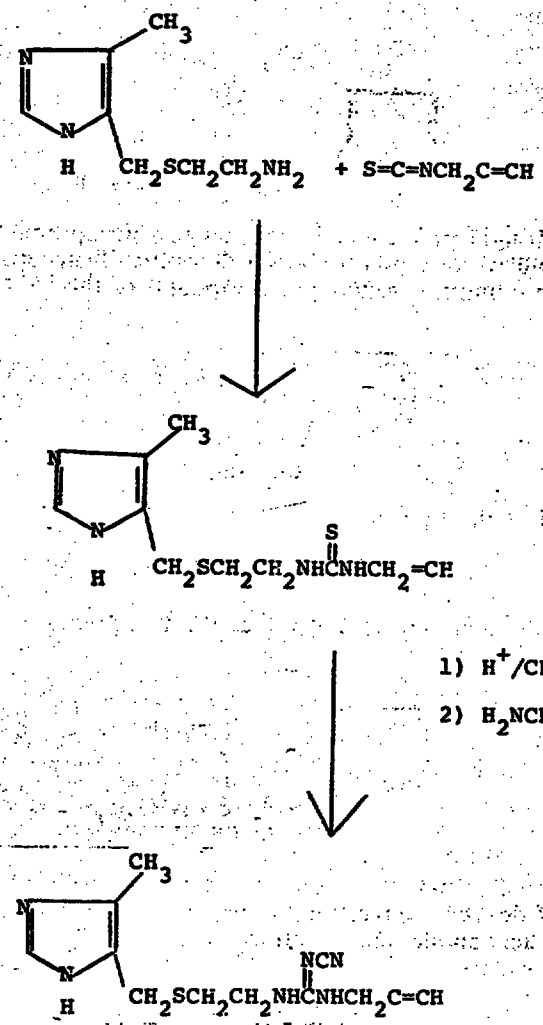


VI

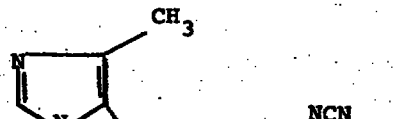
which is then reacted with methyl iodide and cynamide to produce compound I in basic form and, if desired, converting the product to the corresponding nontoxic pharmaceutically acceptable acid addition salt.

This process is illustrated by the following reaction scheme III for a preferred compound of the invention.

Scheme III

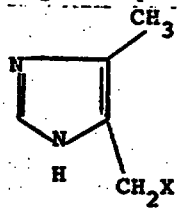


The invention further provides a process for the preparation of a compound of the formula



I

wherein R^1 is a straight or branched chain alkynyl group containing from 3 to 9 carbon atoms, inclusive, or a non-toxic pharmaceutically acceptable acid addition salt thereof characterized by reacting a compound of the formula



VII

or an acid addition salt thereof in which X is hydroxy or a leaving group with a compound of the formula



VIII

wherein R^1 is as defined above and, if desired, converting the resulting compound of formula I in basic form or an acid addition salt thereof to the corresponding non-toxic pharmaceutically acceptable acid addition salt or free base form.

The reaction is conducted in an inert organic solvent.

In a preferred embodiment equimolar quantities of the compounds of formulae VII and VIII are used and the reaction is carried out in the presence of a base.

Suitable leaving groups "X" for use in this reaction are well-known to those skilled in the art. They include, for example, fluoro, chloro, bromo, iodo, $-O_3SR^2$ wherein R^2 is (lower)alkyl [e.g. methanesulfonyloxy], $-O_3SR^3$ wherein R^3 is aryl or substituted aryl [e.g. benzenesulfonyloxy, *p* - bromobenzenesulfonyloxy or *p* - toluenesulfonyloxy], $-O_3SF$, acetoxy and 2,4 - dinitrophenoxy. For convenience and economy we normally prefer to utilize compound VII in which X is chloro.

In the process of this invention, the compound of Formula VII preferably is utilized in the form of an acid addition salt. Compound VII is relatively unstable in its free base form and therefore is preferably prepared and stored as an acid addition salt. Although the free base of the compound of Formula VII may be regenerated prior to the reaction, no advantage is obtained by so doing. It will be appreciated by those skilled in the art that any inorganic acid or organic acid may be utilized to form the acid addition salt of compound VII, e.g. hydrochloric, sulfamic, sulfuric, oxalic, benzoic, succinic, acetic, nitric or citric acid. For convenience and economy we normally prefer to utilize compound VII in the form of its hydrochloride.

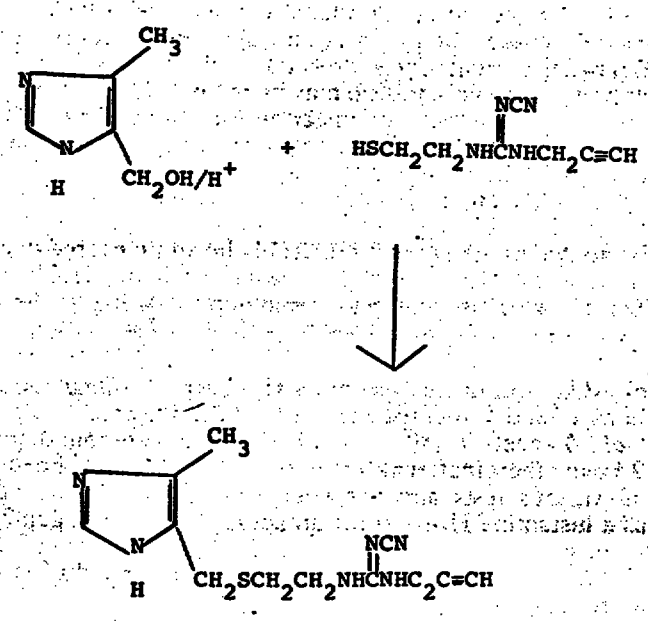
The reaction of compounds VII and VIII to produce compound I may be conducted in any inert organic solvent such as an alkanol, acetonitrile, dimethylformamide, dimethylsulfoxide or acetone. We prefer to conduct the reaction in an alkanol such as ethanol or 2-propanol.

The reaction temperature is not critical; the reaction may be conducted at temperatures of from about 0° to about 200°. At low temperatures the reaction is slow, while high temperatures normally lead to less pure products due to decomposition and the formation of side-products. We normally prefer to conduct the reaction at room temperature.

The reaction of compounds VII and VIII to produce compound I is preferably conducted in the presence of a base, which facilitates the reaction by acting as an acid acceptor. Suitable bases for use in this reaction include both inorganic and organic bases such as NaOH, KOH, LiOH, triethylamine, dimethylaniline and sodium ethoxide.

This process is illustrated by the reaction scheme IV illustrated below for a preferred compound of the invention.

Scheme IV



The intermediates of the formula

$$HSCH_2CH_2NHC(=NCN)NH—R^1 \quad \text{VIII}$$

wherein R^1 is a straight or branched chain alkynyl group containing from 3 to 9 carbon atoms, inclusive, processes for their preparation and acid addition salts thereof, which are useful in the preparation of histamine H_2 receptor antagonists of Formula I, are described and claimed in our co-pending patent application No. 18923/80, (Serial No. 1598630).

The dimethyl cyanodithioiminocarbonate which is used as a starting material for the preparation of the N - cyano - N' - alkynyl - S - methylisothioureas may itself be prepared by procedures described in J. Org. Chem., *32*, 1566 (1967). The alkynylamine starting materials are either commercially available or may be prepared by methods described in Bull. Soc. Chim. Fr., 490 (1958); Bull Soc. Chim. Fr., 592 (1967) and Annales de Chimie (Paris), *3*, 656 (1958).

When reacting cysteamine hydrochloride with an N - cyano - N' - alkynyl - S - methylisothiourea to produce an N - cyano - N' - alkynyl - N" - (2 - mercaptoethyl)guanidine of Formula VIII, it was found desirable to conduct the reaction in the presence of a small amount of hydroquinone and to bubble nitrogen through the reaction mixture (see, for example, step B of Example 14. These reaction conditions were found to produce compounds of Formula VIII in higher yield and of higher purity. The nitrogen sweep is believed to remove the methyl mercaptan produced in the reaction and thereby avoid secondary reactions arising from the addition of methyl mercaptan to the carbon-carbon triple bond. It is believed that the hydroquinone prevents the formation of free radicals and secondary reactions arising from their presence.

As used herein, the term non-toxic pharmaceutically acceptable acid addition salt means the mono- or di-salt of a compound of this invention with a nontoxic pharmaceutically acceptable organic or inorganic acid. Such acids are well known and include hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric, maliec, fumaric succinic, oxalic, benzoic, methanesulfonic, 1,2-ethanedisulfonic, benzenesulfonic, acetic, propionic, tartaric, citric and d-camphorsulfonic acids. The salts are made by methods known in the art.

As used herein the term "(lower) alkyl" is intended to mean straight or branched alkyl groups containing from 1 to 6 carbon atoms.

For therapeutic use, the pharmacologically active compounds of this invention will normally be administered as a pharmaceutical composition comprising as the (or an) essential active ingredient at least one such compound in the basic form or in the form of a nontoxic pharmaceutically acceptable acid addition salt, in association with a pharmaceutically acceptable carrier or diluent.

The pharmaceutical compositions may be adminstered orally, parenterally or by rectal suppository. A wide variety of pharmaceutical forms may be employed. Thus, if a solid carrier is used, the preparation may be tableted, placed in a hard gelatin capsule in powder or pellet form, or in the form of a troche or lozenge. If a liquid carrier is employed, the preparation may be in the form of a syrup, emulsion, soft gelatin capsule, sterile solution for injection, or an aqueous or nonaqueous liquid suspension. The pharmaceutical compositions are prepared by conventional techniques appropriate to the desired preparation.

Preferably, each dosage unit will contain the active ingredient in an amount of from about 50 mg. to about 250 mg., and most preferably from about 100 mg. to about 200 mg. The active ingredient will preferably be administered in equal doses from two to four times a day. The daily dosage regimen will preferably be from 250 mg. to about 1000 mg., and most preferably from about 500 mg. to about 750 mg.

Histamine H_2-receptor antagonists have been shown to be effective inhibitors of gastric secretion in animals and man, Brimblecombe *et al.*, J. Int. Med. Res., *3*, 86 (1975). Clinical evaluation of the histamine H_2-receptor antagonist cimetidine has shown it to be an effective therapeutic agent in the treatment of peptic ulcer disease, Gray *et al.*, Lancet, *1* (8001), 4 (1977). The compound prepared in Examples 1 and 2 below (hereinafter referred to as BL-5641) has been compared with cimetidine in various tests and has been shown to be more potent than cimetidine both as a histamine H_2-receptor antagonist in isolated guinea pig atria and as an inhibitor or gastric secretion in rats and dogs. Furthermore, the gastric secretion studies in dogs indicate that BL-5641 has a longer duration of activity than cimetidine at equal doses.

Histamine H_2-Receptor Antagonism-isolated Guinea Pig Atria Assay

Histamine produces concentration-related increases in the contractile rate of isolated, spontaneously beating guinea pig right atria. Black *et al.*, Nature, *236*, 385 (1972), described the receptors involved in this effect of histamine as histamine H_2-receptors when they reported the properties of burimamide, a competitive antagonist of these receptors. Subsequent investigations by Hughes and Coret, Proc. Soc. Exp. Biol. Med., *148*, 127 (1975) and Verma and McNeill, J. Pharmacol. Exp. Ther., *200*, 352 (1977) support the conclusion of Black and coworkers that the positive chronotropic effect of histamine in isolated guinea pig right atria is mediated via histamine H_2-receptors. Black et al., Agents and Actions, *3*, 133 (1973) and Brimblecombe et al., Fed. Proc., *35*, 1931 (1976) have utilized isolated guinea pig right atria as a means for comparing the activities of histamine H_2-receptor antagonists. The present comparative studies were carried out using a modification of the procedure reported by Reinhardt et al., Agents and Actions, *4*, 217 (1974).

Male Hartley strain guinea pigs (350—450 gm.) were sacrificed by a blow on the head. The heart was excised and placed in a Petri dish of oxygenated (95% O_2, 5% CO_2) modified Krebs solution (g./liter: NaCl 6.6, KCl 0.35, $MgSO_4 \cdot 7H_2O$ 0.295, KH_2PO_4 0.162, $CaCl_2$ 0.238, $NaHCO_3$ 2.1 and dextrose 2.09). The spontaneously beating right atrium was dissected free from other tissues and a silk thread attached to each end. The atrium was suspended in a 20 ml. muscle chamber containing oxygenated modified Krebs solution maintained at 32°C. Atrial contractions were recorded isometrically by means of a Grass FT 0.03 force displacement transducer and recordings of contractile force and rate were made with a Beckman RP Dynograph.

A resting tension of 1 g. was applied to the atrium and it was allowed to equilibrate for 1 hour. At the end of the equilibration period a submaximal concentration of histamine dihydrochloride (3×10^{-6}M) was added to the bath and washed out to prime the tissue. Histamine was then added to the bath in a cumulative fashion using 1/2 log 10 intervals to give final molar bath concentrations of 1×10^{-7} to 3×10^{-5}. The histamine-induced increase in a trial rate was allowed to plateau before the next successive concentration was added. The maximal response invariably occurred at the 3×10^{-5}M concentration. The histamine was washed out several times and the atrium allowed to return to control rate. The test compound (1×10^{-5}M) was then added and after a 30 minute incubation the histamine concentration-response was repeated, adding higher concentrations as needed.

The histamine ED50 values (concentration of histamine which increased contractile rate 50% of maximum) and 95% confidence limits before and after the test compound administration were obtained by regression analysis as described by Finney, Probit Analysis, 3rd ed., Cambridge (1971). Concentration-response curve displacement factors were calculated as follows:

$$\text{Displacement Factor} = \frac{\text{ED50 Histamine+Compound}}{\text{ED50 Histamine Alone}}$$

The factor obtained for BL-5641 was then expressed as a ratio of the factor obtained for cimetidine.

$$\text{Activity Ratio} = \frac{\text{BL-5641 Displacement Factor}-1}{\text{Cimetidine Displacement Factor}-1}$$

The results obtained from these studies are summarized in Table 1. Cimetidine and BL-5641 displaced the histamine concentration-response curve to the right by a factor of 6.6 and 32.7, respectively. Based on the concentration-response curve displacement factors, BL-5641 was about 5.7 times more active than cimetidine as a histamine H_2-receptor antagonist in isolated guinea pig right atria.

(19)

TABLE I

Relative Activity of Cimetidine and BL-5641 in Isolated Guinea Pig Right Atria

Compound	N	Concentration	Histamine ED50 With 95% Confidence Limits (μg/ml.)	Concentration-Response Curve Displacement Factor	Activity Ratio
Histamine Control	3		0.21 (0.18—0.25)	—	—
Cimetidine	3	1×10^{-5}M	1.39 (1.08—1.85)	6.6	1.0
Histamine Control	2		0.38 (0.27—0.53)	—	—
BL-5641	2	1×10^{-5}M	12.44 (7.81—20.28)	32.7	5.7

N=number of experiments.

Determination of Gastric Antisecretory Activity in the Two Hour Pylorus Ligated (Shay) Rat

The pyloric ligation procedure in the rat was designed by Shay et al., Gastroenterology, *5*, 53 (1945) for the study of perforating gastric ulcers; however, as the method become known, it was also employed as a means of studying rat gastric secretion, Shay et al., Gastroenterology, *26*, 906 (1954), Brodie, D. A., Am. J. Dig. Dis., *11*, 231 (1966). A modification of this procedure is presently used to evaluate compounds for gastric antisecretory activity.

Male Long Evans rats, 280—300 gm., are used. The animals are placed in individual cages and fasted for 24 hours with free access to water. Under ether anesthesia, the stomach is reached through a midline incision, and a cotton-thread ligature is placed around the pylorus, After wound closure, ether administration is stopped and BL-5641, cimetidine or vehicle is adminstered intraperitoneally in a volume of 1 mg./kg. BL-5641 and cimetidine are solubilized with one equivalent of HCl and brought to the desired volume with water. The animals are returned to their cages from which the water bottles have been removed and two hours later are sacrificed with ether. The stomach is removed and the two hour gastric collection is drained into a graduated test tube for volume determination. Titratable acidity is measured by titrating a one ml. sample to pH 7.0 with 0.02N NaOH, using an Autoburet and an electrometric pH meter (Radiometer). Titratable acid output is calculated in microequivalents by multiplying the volume in milliliters by the acid concentration in milliequivalents per liter. The percent inhibition of acid output is calculated as follows

$$\%\ \text{Inhibition Acid Output} = \frac{\text{Acid Output-Control} - \text{Acid Output-Drug}}{\text{Acid Output-Control}} \times 100$$

The results obtained with BL-5641 and cimetidine are presented in Table 2. These results indicate that, in the two hour pylorus ligated rat preparation, BL-5641 is at least as potent as cimetidine with respect to the inhibition of gastric acid output.

TABLE 2
Effect of BL-5641 and Cimetidine on Gastric Acid Output in the Two Hour Pylorus Ligated Rat

Compound	Dose (ip)[a] μMole/kg.	Dose (ip)[a] mg./kg.	% Inhibition of Acid Output	ED50 μMole/kg.
BL-5641	40	11.1	80	~11
	20	5.53	61	
	10	2.76	37	
Cimetidine	40	10	66	~14
	20	5	60	
	10	2.5	40	
	5	1.25	34	

[a]At least 5 animals were employed at each dose.

Determination of Gastric Antisecretory Activity in the Gastric Fistula Dog

Thomas type [Thomas, J. E., Proc. Soc. exp. Biol. Med., *46*, 260 (1941)] stainless steel cannulae are inserted into the stomachs of beagle dogs (10—12 kg.) just orad to the pyloric gland area near the greater curvature to provide a chronic gastric fistula. Animals are allowed to recover for at least two months before any testing is done. Dogs are fasted overnight (~18 hours) with water *ad lib* prior to each experiment. The dogs are placed in a sling and an eight inch inside needle catheter (C. R. Baird, Inc.) with a two inch 17 gauge needle is inserted into a leg vein for purposes of drug administration. Gastric secretions are collected every 15 minutes by gravity drainage from the opened cannula. Basal secretions are collected for two consecutive 15 minute periods and if these prove to be excessive (>4 ml./15 min.; pH <5.0) the animal is not used. A modification of the procedure described by Grossman and Konturek, Gastroenterology, *66*, 517 (1974) was followed. Immediately after the second basal collection, histamine (100 μg./kg./hr.) is infused for 90 minutes with a Harvard Infusion Pump in a volume of 6 ml./hr. At this time BL-5641, cimetidine (solubilized with one equivalent of HCl and brought a proper volume with normal saline) or normal saline is injected rapidly (within 30 seconds) in a volume of 0.1 ml./kg. and then infusion of histamine continues for an additional 150 minutes (total time of infusion is 4 hours). Each 15 minute sample of gastric juice is measured to the nearest 0.5 ml. and titratable acidity against 0.02N NaOH (endpoint pH 7.0) is measured with an Autoburet and pH meter (radiometer). The percent inhibition of acid output is calculated as described in the pylorus ligated rat procedure.

Equimolar doses of BL-5641 and cimetidine were administered to five different dogs and the results obtained are presented in Table 3.

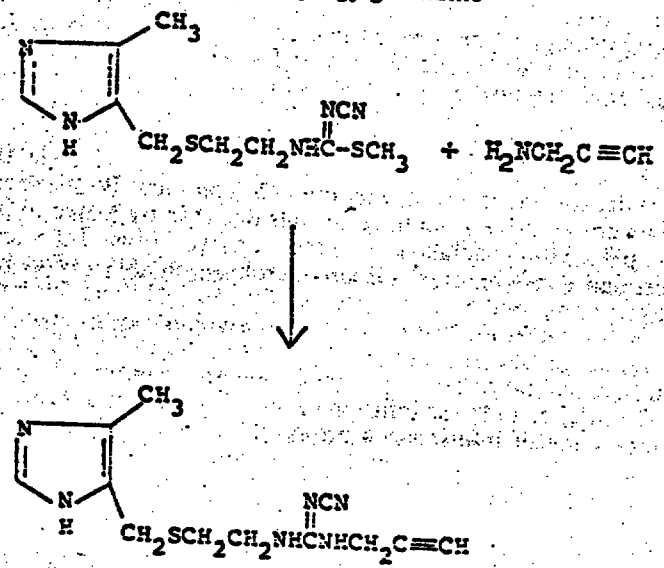
Both BL-5641 and cimetidine produced an immediate inhibitory effect on gastric acid output. However, the degree of inhibition at equimolar doses was consistently greater and of longer duration with BL-5641 than with cimetidine. These results indicate that as an inhibitor of histamine-induced gastric acid output in the dog, BL-5641 is more potent and/or longer acting than cimetidine.

The invention is illustrated but in no way limited by the following Examples. The temperatures given therein are in degrees Centrigrade.

TABLE 3
Effect of BL-5641 and Cimetidine on Gastric Acid Output in Conscious Gastric Fistula Dogs

Drug & Dose (μM/kg. iv)	Dog No.	% Inhibition Acid Output (N=1) 15	30	45	60	75	90	105	120 min.
BL-5641 (12)	24136	66	99	99	99	99	93	91	73
Cimetidine (12)	24136	63	99	89	76	54	48	41	14
BL 5641 (6)	22619	82	99	99	95	78	76	52	53
Cimetidine (6)	22619	84	96	73	67	65	54	40	32
BL-5641 (3)	23606	60	59	36	34	32	42	24	0
Cimetidine (3)	23606	43	27	15	0	17	38	8	0
BL-5641 (1.5)	24895	82	72	53	49	33	7	0	0
Cimetidine (1.5)	24895	73	57	60	29	0	18	0	0
BL-5641 (0.75)	23553	51	38	28	28	31	43	42	46
Cimetidine (0.75)	23553	50	10	24	17	35	27	25	19

Example 1
N-Cyano-N'-[2-[(4-methyl-5-imidazolyl)methylthio]ethyl]-N"-propargylguanidine

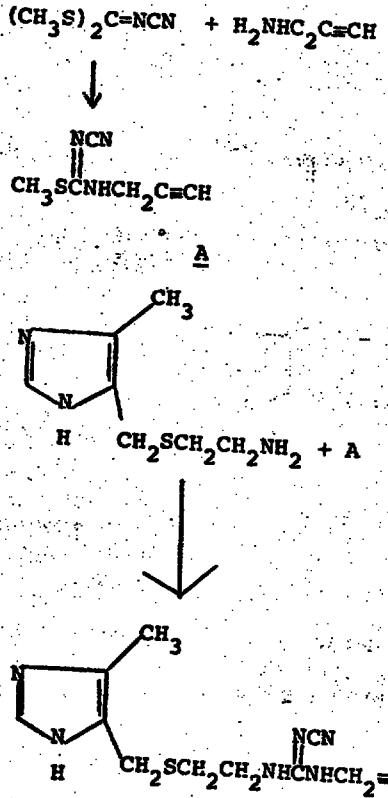


A mixture of N - cyano - N' - [2 - [(4 - methyl - 5 - imidazolyl)methylthio]ethyl] - S - methyl - isothiourea (3.00 g, 0.0111 mole) and propargylamine (2.50 g, 0.045 mole) in acetonitrile (60 ml) was stirred at reflux for 65 hours, and then was heated in a stainless steel pressure vessel at 120—130° for 38 hours. The reaction mixture was cooled, decanted from a tar, and then evaporated to leave a gum (3.57 g). This material was placed on silica gel (100—200 mesh) and eluted with a mixture of methylene chloride (97 parts) and methanol (3 parts). The product obtained from a middle fraction was crystallized by trituration under acetonitrile, and then was recrystallized from acetonitrile to yield the title compound (0.236 g; 7.7%) mp 146—149.5°.

Anal. Calc'd for $C_{12}H_{16}N_6S$: C, 52.15; H, 5.83; N, 30.41.
Found: C, 51.86; H, 5.81; N, 30.70.

Example 2

N-Cyano-N'-[2-[(4-methyl-5-imidazolyl)methylthio]ethyl]-N"-propargylguanidine



a. N-Cyano-N'-propargyl-S-methyl-isothiourea (A).

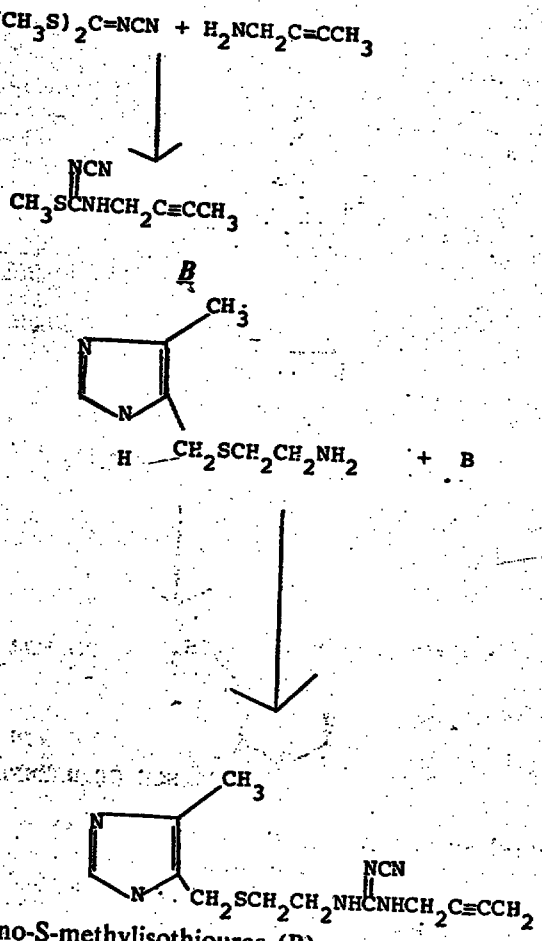
A solution of dimethyl cyanodithioiminocarbonate (16.00 g, 0.109 mole) and propargylamine (6.03 g, 0.109 mole) in acetonitrile (320 ml) was stirred at reflux for 4 hours, and then at 25° for 12 hours. Workup gave the title compound A (13,58 g, 81%), mp 160—164°.

b. N-cyano-N'-[2-[(4-methyl-5-imidazolyl)methylthio]ethyl]-N"-propargylguanidine

A solution of *A* (11.71 g, 0.0765 mole) and 2-[(4-methyl-5-imidazolyl)methylthio]ethylamine (13.10 g, 0.0765 mole) in methanol (250 ml) was heated at reflux for 64 hours. The solvent was removed by evaporation, the residue placed on silica gel (100—200 mesh) and chromatographed by gradient elution using methylene chlorine/methanol; the latter fractions yielded 4.0 g of the title compound. Recrystallization from acetonitrile gave purified product mp 150—152.5° identical (ir, nmr, tlc) with the product prepared in Example 1.

Example 3

N-Cyano-N'-[2-[(4-methyl-5-imidazolyl)methylthio]ethyl]-N"-(2-butyn-1-yl)guanidine



a. N-(2-Butyn-1-yl)-N'-cyano-S-methylisothiourea (B)

A solution of dimethyl cyanodithioiminocarbonate (10.00 g, 0.0684 mole) and 2-butyn-1-ylamine (4.73 g, 0.0684 mole) in acetonitrile (200 ml) was stirred at 25° for 0.5 hour, and then at reflux for 2.5 hours. The mixture was cooled, then filtered to yield the title compound *B*, mp 180—183°.

b. N-Cyano-N'-[2-[(4-methyl-5-imidazolyl)methylthio]ethyl]-N"-(2-butyn-1-yl)guanidine

A solution of *B* (6.82 g, 0.0407 mole) and 2 - [(4 - methyl - 5 - imidazolyl)methylthio]ethylamine (6.98 g, 0.0407 mole) in methanol (140 ml) was heated at reflux for 40 hours. Workup and chromatography as described above for Example 2 yielded the title compound. When the title compound was prepared according to the general procedure of Example 1, it melted at 128—130°.

Example 4

N-Cyano-N'-[2-[(4-methyl-5-imidazolyl)methylthio]ethyl]-N"-(3-butyn-1-yl)guanidine

The general procedure of Example 1 is repeated except that the propargylamine utilized therein is replaced by an equimolar amount of 3-butyn-1-ylamine, and the title product is thereby produced.

Example 5

N-Cyano-N'-[2-[(4-methyl-5-imidazolyl)methylthio]ethyl]-N"-(4-pentyn-1-yl)guanidine

The general procedure of Example 1 is repeated except that the propargylamine utilized therein is replaced by an equimolar amount of 4-pentyn-1-ylamine, and the title product is thereby produced; m.p. 99—103°.

Example 6

N-Cyano-N'-[2-[(4-methyl-5-imidazolyl)methylthio]ethyl]-N"-(2-methyl-3-butyn-2-yl)guanidine

The general procedure of Example 3 is repeated except that the 2-butyn-1-ylamine utilized therein is replaced by an equimolar amount of 1,1-dimethylpropargylamine, and the title product is thereby produced.

Example 7

N-Cyano-N'-[2-[(4-methyl-5-imidazolyl)methylthio]ethyl]-N"-(3-butyn-2-yl)guanidine

The general procedure of Example 3 is repeated except that the 2-butyn-1-ylamine utilized therein is replaced by an equimolar amount of 1-methylpropargylamine, and the title product is thereby produced.

Example 8

N-Cyano-N'-[2-[(4-methyl-5-imidazolyl)methylthio]ethyl]-N"-(2-butyn-1-yl)guanidine

A mixture of N - cyano - N' - [2 - [(4 - methyl - 5 - imidazolyl)methylthio]ethyl] - S - methylisothiourea (3.00 g. 0.0111 mole) and 2-butyn-1-ylamine (3.07 g., 0.0445 mole) in 60 ml. of propionitrile was stirred at reflux for 40 hours. TLC assay of an aliquot of the reaction mixture showed a trace of the isothiourea starting material, so the mixture was refluxed for an additional 6 hours and then stirred at room temperature for 64 hours. The solvent (along with excess amine) was removed at reduced pressure and the residual gum was placed on silica gel (100—200 mesh) and eluted with a mixture of methylene chloride (97 parts) and methanol (3 parts). The middle fractions were combined and evaporated to give 1.81 g. of yellow gum. The gum was dissolved in 20 ml. of ethyl acetate and crystallized at −15°C. The resulting pale yellow solid (1.2 g.) was dissolved in 11 ml. of hot acetonitrile and recrystallized at −15°C; yield 1.072 g., m.p. 128—130°C.

Anal. Calc'd for $C_{13}H_{18}N_6S$:

C, 53.77; H, 6.25; N, 28.94; S, 11.08

Found: C, 53.72; H, 6.29; N, 29.62; S, 11.34

Example 9

N-Cyano-N'-[2-[(4-methyl-5-imidazolyl)methylthio]ethyl]-N"-(3-butyn-1-yl)guanidine

A mixture of N - cyano - N' - [2 - [(4 - methyl - 5 - imidazolyl)methylthio]ethyl]-S - methylisothiourea (3.00 g., 0.0111 mole) and 3-butyn - 1 - ylamine (3.13 g., 0.0453 mole) in 60 ml. of propionitrile was stirred at reflux for 40 hours. The solvent was evaporated to give 5.40 g. of a syrup which was placed on 70 g. of 100—200 mesh silica gel and chromatographed by gradient elution using methylene chloride/methanol.

Fraction	Eluant	Volume	Weight
1	99 CH_2Cl_2/1 MeOH	100 ml.	—
2	"	70 ml.	—
3	"	50 ml.	0.117 g.
4	"	30 ml.	—
5	"	75 ml.	0.067 g.
6	"	150 ml.	0.080 g.
7	"	325 ml.	0.168 g.
8	98 CH_2Cl_2/2 MeOH	50 ml.	—
9	"	150 ml.	0.125 g.
10	"	250 ml.	0.811 g.
11	"	250 ml.	0.72 g.
12	97 CH_2Cl_2/3 MeOH	175 ml.	0.125 g.
13	"	225 ml.	0.133 g.
14	"	—	0.027 g.
15	"	225 ml.	0.002 g.
16	"	200 ml.	
17	95 CH_2Cl_2/5 MeOH	250 ml.	0.035 g.
18	"	250 ml.	0.236 g.

TLC (silica gel, 90 CH_2Cl_2/10 MeOH) indicated fractions 9—12 were pure and should be combined. Fractions 1—8 showed fast moving impurities. Fractions 13 and 14 showed some trailing impurities. Fractions 9—12 were combined and evaporated to 1.72 g. of a yellow gum. The gum was dissolved in 11 ml. of nitromethane, crystallized at −15°C (pale yellow solid, 1.18 g.), and recrystallized from 9 ml. of nitromethane to give 0.987 gm.; m.p. 86—89°C (softens at 85°C). Infrared and NMR (100 MHZ) were clean and consistent with the desired structure. NMR showed that the product was solvated with approximately 0.08 mole of nitromethane.

Anal. Calc'd for $C_{13}H_{18}N_6S \cdot 0.08\ (CH_3NO_2)$:
C, 53.21; H, 6.22; N, 28.84; S, 10.86
Found: C 52.68, 52.87; H, 6.28, 6.02, N, 29.39, 29.50; S, 11.22

Example 10

N-Cyano-N′-[2-[(4-methyl-5-imidazolyl)methylthio]ethyl]-N″-(4-pentyn-1-yl)guanidine

A mixture of N - cyano - N′ - [2-[(4 - methyl - 5 - imidazolyl)methylthio]ethyl] - S - methylisothiourea (3.00 g., 0.0111 mole) and 4 - pentyn - 1 - ylamine (3.69 g., 0.0445 mole) in 60 ml. of acetonitrile was stirred at reflux for 24 hours, and then allowed to stand at room temperature for 96 hours. The solvent and excess amine were removed under reduced pressure and the residual yellow gum was purified by chromatography on 50 g. of 100—200 mesh silica gel, using gradient elution with methylene chloride/methanol (99:1—96:4). The middle fractions indicated by TLC to be pure were combined and evaporated to give 1.91 g. of yellow gum which was crystallized at −15°C from 18 ml. of ethyl acetate. The resulting white solid (1.25 g.) was recrystallized at −15°C from 10 ml. of acetonitrile to give 1.063 g. of product; m.p. 99—103°C.

Anal. Calc'd for $C_{14}H_{20}N_6S$:
C, 55.24; H, 6.52, N, 27.61; S, 10.53
Found: C, 55.43; H, 6.58, N, 28.26; S, 10.97

Example 11

N-Cyano-N′-[2-[(4-methyl-5-imidazolyl)methylthio]ethyl]-N″-propargylguanidine

The mixture of N - cyano - N′ - [2 - [(4 - methyl - 5 - imidazolyl)methylthio]ethyl] - S - methylisothiourea (10.0 g; 0.0371 mole) and distilled propargylamine (20 ml; 0.325 mole) in methanol (50 ml) was stirred at reflux, under a positive pressure nitrogen atomosphere (nitrogen sweep), for 20.5 hours. The solvent and excess amine were then removed by evaporation to leave a yellow-brown oil that readily crystallized. Trituration of the crude product under isopropanol (30 ml) gave the title compound as an off-white, friable solid (8.11 g, 79%); m.p. 146—148.5°.

Example 12

N-Cyano-N′-[2-[(4-methyl-5-imidazolyl)methylthio]ethyl]-N″-propargylguanidine

A mixture of N - cyano - N′ - [2-[(4 - methyl - 5 - imidazolyl)methylthio]ethyl] - S - methylisothiourea (100 g; 0.371 mole) and distilled propargylamine (150 ml; 2.44 moles) in methanol (500 ml) was stirred at reflux under a positive pressure nitrogen atmosphere (nitrogen sweep) for 22 hours. The reaction mixture was cooled, and the solvent and excess amine were removed by evaporation to leave an amber oil that readily crystallized. The crude product was triturated under isopropanol (250 ml), cooled at 0° for 2 hours and collected by filtration. The filter cake was washed with cold isopropanol and dried *in vacuo* over P_2O_5 for 16 hours. The dried title product was a near-white dense solid; yield 73.5 gm. (71.7%) m.p. 147—149°.

Example 13

Recrystallization of N-Cyano-N′-[2-[(4-methyl-5-imidazolyl)-methylthio]ethyl]-N″-propargylguanidine

The final products obtained in Examples 11 and 12 were combined (total 81.3 g.), dissolved in hot isopropanol (1000 ml.), filtered through "Super-Cel" (Registered Trade Mark) and allowed to cool at room temperature for ca. 68 hours.

The resulting crystalline product was recovered by filtration, washed with cold isopropanol, pulverized and dried in a heated desiccator under high vacuum for ca. 45 hours. Yield 72.4 g. (89% recovery); m.p. 149—151°. HPLC assay showed the purity to be ca. 99.5%. The NMR (100 MHz) spectrum was clean and consistent.

Anal. Calc'd for $C_{12}H_{16}N_6S$: C, 52.15; H, 5.83; N, 30.41; S, 11.60
Found: C, 52.42; H, 5.94; N, 30.51; S, 11.35

Example 14

N-Cyano-N'-[2-[(4-methyl-5-imidazolyl)methylthio]ethyl]-N"-propargylguanidine

A. N-Cyano-N'-propargyl-S-methylisothiourea

A solution of dimethyl cyanodithioiminocarbonate (16.00 g, 0.109 mole) and propargylamine (6.03 g, 0.109 mole) in acetonitrile (320 ml) was stirred at reflux for 4 hours, and then at 25° for 12 hours. The mixture was cooled and filtered to yield the title compound (13.58 g, 81%), m.p. 160—164°.

B. N-Cyano-N'-propargyl-N"-(2-mercaptoethyl)guanidine

A mixture of 1.136 g. (10 m moles) of cysteamine hydrochloride, 1.53 g. (10 m moles) of the product of step A, above, and 0.055 g. of hydroquinone in 10 ml. DMF was slightly warmed to dissolve the compounds. To this solution was added 10 ml. of 1N aqueous sodium hydroxide and nitrogen was bubbled through the solution. After standing at room temperature for 17 hours, the reaction mixture was evaporated to dryness to give a mixture of the title product and sodium chloride. The title product was extracted from this mixture with 10 ml. of ethanol and the ethanolic solution was used in step C, below.

C. N-Cyano-N'-[2-[(4-methyl-5-imidazolyl)methylthio]ethyl]-N"-propargylguanidine

The ethanol solution of the product of step B, above, (about 10 m moles) was added to a solution of 0.46 g sodium (0.02 g-atoms) in 10 ml ethanol at 4°C under nitrogen. After 5 minutes, a solution of 1.67 g. (10 m moles) of 4-methyl-5-chloromethylimidazole · HCl in 14 ml. ethanol was added and the mixture was stirred at room temperature under nitrogen for 70 minutes. The reaction mixture was filtered through a bed of Celite (Registered Trade Mark) filter aid to remove the inorganic salts and the Celite was washed with ethanol. The filtrate was evaporated to dryness and the product was purified by chromatography on a silica gel column (20 g silica, 3.2×4.5 cm bed) with ethanol-chloroform mixtures as the solvent. The ethanol content was gradually increased from 2 to 15%. The eluant was evaporated to dryness to give 1.906 g of crystalline product. Recrystallization from 2-propanol gave 1.49 g. (54%) of the title product, m.p. 144—145°C.

Example 15

N-Cyano-N'-[2-[(4-methyl-5-imidazolyl)methylthio]ethyl]-N"-(2-butyn-1-yl)guanidine

A. N-Cyano-N'-(2-butyn-1-yl)-S-methylisothiourea

A solution of dimethyl cyanodithioiminocarbonate (10.00 g., 0.0684 mole) and 2-butyn-1-ylamine (4.73 g., 0.0684 mole) in acetonitrile (200 ml.) was stirred at 25° for 0.5 hour, and then at reflux for 2.5 hours. The mixture was cooled, then filtered to yield the title compound, m.p. 180—183°.

B. N-Cyano-N'-(2-butyn-1-yl)-N"-(2-mercaptoethyl)guanidine

The general procedure of Example 14B is repeated except that the N - cyano - N' - propargyl - S - methylisothiourea utilized therein is replaced by an equimolar amount of N - cyano - N' - (2 - butyn - 1 - yl) - S - methylisothiourea, and the title product is thereby produced.

C. N-Cyano-N'-[2-[(4-methyl-5-imidazolyl)methylthio]ethyl]-N"-(2-butyn-1-yl)guanidine

The general procedure of Example 14C is repeated except that the N - cyano - N' - propargyl - N" - (2 - mercaptoethyl)guanidine utilized therein is replaced by an equimolar amount of N - cyano - N' - (2 - butyn - 1 - yl) - N" - (2 - mercaptoethyl)guanidine, and the title product is thereby produced.

Example 16

N-Cyano-N′-[2-[(4-methyl-5-imidazolyl)methylthio]ethyl]-N″-(3-butyn-1-yl)guanidine

A. N-Cyano-N′-(3-butyn-1-yl)-N″-(2-mercaptoethyl)guanidine

The general procedures of Example 14 steps A and B, are repeated except that the propargylamine utilized in step A thereof is replaced by an equimolar amount of 3 - butyn - 1 - ylamine, and the title product is thereby produced.

B. N-Cyano-N′-[2-[(4-methyl-5-imidazolyl)methylthio]ethyl]-N″-(3-butyn-1-yl)guanidine

The general procedure of Example 14C is repeated except that the N - cyano - N′ - propargyl - N″ - (2 - mercaptoethyl)guanidine utilized therein is replaced by an equimolar amount of N - cyano - N′ - (3 - butyn - 1 - yl) - N″ - (2 - mercaptoethyl)guanidine, and the title product is thereby produced.

Example 17

N-Cyano-N′-[2-[(4-methyl-5-imidazolyl)methylthio]ethyl]-N″-(4-pentyn-1-yl)guanidine

A. N-Cyano-N′-(4-pentyn-1-yl)-N″-(2-mercaptoethyl)guanidine

The general procedures of Example 14, steps A and B, are repeated except that the propargylamine utilized in step A thereof is replaced by an equimolar amount of 4 - pentyn - 1 - ylamine, and the title product is thereby produced.

B. N-Cyano-N′-[2-[(4-methyl-5-imidazolyl)methylthio]ethyl]-N″-(4-pentyn-1-yl)guanidine

The general procedure of Example 14C is repeated except that the N - cyano - N′ - propargyl - N″ - (2 - mercaptoethyl)guandine utilized therein is replaced by an equimolar amount of N - cyano - N′ - (4 - pentyn - 1 - yl) - N″ - (2 - mercaptoethyl)guanidine, and the title product is thereby produced.

Example 18

N-Cyano-N′-[2-[(4-methyl-5-imidazolyl)methylthio]ethyl]-N″-(2-methyl-3-butyn-2-yl)guanidine

A. N-Cyano-N′-(2-methyl-3-butyn-2-yl)-N″-(2-mercaptoethyl)guanidine

The general procedures of Example 14, steps A and B, are repeated except that the propargylamine utilized in step A thereof is replaced by an equimolar amount of 1,1-dimethylpropargylamine, and the title product is thereby produced.

B. N-Cyano-N′-[2-[(4-methyl-5-imidazolyl)methylthio]-ethyl]-N″-(2-methyl-3-butyn-2-yl)guanidine

The general procedure of Example 14C is repeated except that the N - cyano - N′ - propargyl - N″ - (2 - mercaptoethyl)guanidine utilized therein is replaced by an equimolar amount of N - cyano - N′ - (2 - methyl - 3 - butyn - 2 - yl) - N″ - (2 - mercaptoethyl)guanidine, and the title product is thereby produced.

Example 19

N-Cyano-N′-[2-[(4-methyl-5-imidazolyl)methylthio]ethyl]-N″-(3-butyn-2-yl)guanidine

A. N-Cyano-N′-(3-butyn-2-yl)-N″-(2-mercaptoethyl)guanidine

The general procedures of Example 14 steps A and B, are repeated except that the propargylamine utilized in step A thereof is replaced by an equimolar amount of 1-methyl-propargylamine, and the title product is thereby produced.

B. N-Cyano-N′-[2-[(4-methyl-5-imidazolyl)methylthio]ethyl]-N″-(3-butyn-2-yl)guanidine

The general procedure of Example 14C is repeated except that the N - cyano - N′ - propargyl - N″ - (2 - mercaptoethyl)guanidine utilized therein is replaced by an equimolar amount of N - cyano - N′ - (3 - butyn - 2 - yl) - N″ - (2 - mercaptoethyl)guanidine, and the title product is thereby produced.

WHAT WE CLAIM IS:—

1. A compound of the general formula:

Example 16

N-Cyano-N'-[2-[(4-methyl-5-imidazolyl)methylthio]ethyl]-N"-(3-butyn-1-yl)guanidine

A. N-Cyano-N'-(3-butyn-1-yl)-N"-(2-mercaptoethyl)guanidine

The general procedures of Example 14 steps A and B, are repeated except that the propargylamine utilized in step A thereof is replaced by an equimolar amount of 3 - butyn - 1 - ylamine, and the title product is thereby produced.

B. N-Cyano-N'-[2-[(4-methyl-5-imidazolyl)methylthio]ethyl]-N"-(3-butyn-1-yl)guanidine

The general procedure of Example 14C is repeated except that the N - cyano - N' - propargyl - N" - (2 - mercaptoethyl)guanidine utilized therein is replaced by an equimolar amount of N - cyano - N' - (3 - butyn - 1 - yl) - N" - (2 - mercaptoethyl)guanidine, and the title product is thereby produced.

Example 17

N-Cyano-N'-[2-[(4-methyl-5-imidazolyl)methylthio]ethyl]-N"-(4-pentyn-1-yl)guanidine

A. N-Cyano-N'-(4-pentyn-1-yl)-N"-(2-mercaptoethyl)guanidine

The general procedures of Example 14, steps A and B, are repeated except that the propargylamine utilized in step A thereof is replaced by an equimolar amount of 4 - pentyn - 1 - ylamine, and the title product is thereby produced.

B. N-Cyano-N'-[2-[(4-methyl-5-imidazolyl)methylthio]ethyl]-N"-(4-pentyn-1-yl)guanidine

The general procedure of Example 14C is repeated except that the N - cyano - N' - propargyl - N" - (2 - mercaptoethyl)guandine utilized therein is replaced by an equimolar amount of N - cyano - N' - (4 - pentyn - 1 - yl) - N" - (2 - mercaptoethyl)guanidine, and the title product is thereby produced.

Example 18

N-Cyano-N'-[2-[(4-methyl-5-imidazolyl)methylthio]ethyl]-N"-(2-methyl-3-butyn-2-yl)guanidine

A. N-Cyano-N'-(2-methyl-3-butyn-2-yl)-N"-(2-mercaptoethyl)guanidine

The general procedures of Example 14, steps A and B, are repeated except that the propargylamine utilized in step A thereof is replaced by an equimolar amount of 1,1-dimethylpropargylamine, and the title product is thereby produced.

B. N-Cyano-N'-[2-[(4-methyl-5-imidazolyl)methylthio]-ethyl]-N"-(2-methyl-3-butyn-2-yl)guanidine

The general procedure of Example 14C is repeated except that the N - cyano - N' - propargyl - N" - (2 - mercaptoethyl)guanidine utilized therein is replaced by an equimolar amount of N - cyano - N' - (2 - methyl - 3 - butyn - 2 - yl) - N" - (2 - mercaptoethyl)guanidine, and the title product is thereby produced.

Example 19

N-Cyano-N'-[2-[(4-methyl-5-imidazolyl)methylthio]ethyl]-N"-(3-butyn-2-yl)guanidine

A. N-Cyano-N'-(3-butyn-2-yl)-N"-(2-mercaptoethyl)guanidine

The general procedures of Example 14 steps A and B, are repeated except that the propargylamine utilized in step A thereof is replaced by an equimolar amount of 1-methyl-propargylamine, and the title product is thereby produced.

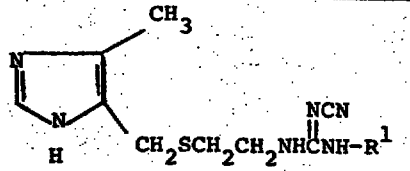
B. N-Cyano-N'-[2-[(4-methyl-5-imidazolyl)methylthio]ethyl]-N"-(3-butyn-2-yl)guanidine

The general procedure of Example 14C is repeated except that the N - cyano - N' - propargyl - N" - (2 - mercaptoethyl)guanidine utilized therein is replaced by an equimolar amount of N - cyano - N' - (3 - butyn - 2 - yl) - N" - (2 - mercaptoethyl)guanidine, and the title product is thereby produced.

WHAT WE CLAIM IS:—

1. A compound of the general formula:

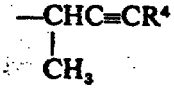
* C L M S *



I

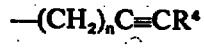
wherein R^1 is a straight or branched chain alkynyl group containing from 3 to 9 carbon atoms, inclusive.

2. A compound as claimed in claim 1 wherein R^1 is



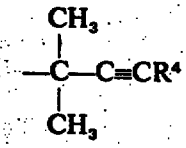
wherein R^4 is H or CH_3.

3. A compound as claimed in claim 1 wherein R^1 is:



wherein R^4 is H or CH_3 and n is an integer of from 1 to 6.

4. A compound as claimed in claim 1 wherein R^1 is:



wherein R^4 is H or CH_3.

5. A compound as claimed in claim 3, wherein n is 1 or 2.

6. A compound as claimed in any one of claims 2 to 5 wherein R^4 is H.

7. A compound as claimed in any one of claims 2 to 5 wherein R^4 is $-CH_3$.

8. N - Cyano - N' - [2 - [(4 - methyl - 5 - imidazolyl)methylthio]ethyl] - N" - (2 - butyn - 1 - yl)guanidine.

9. N - Cyano - N' - [2 - [(4 - methyl - 5 - imidazolyl)methylthio]ethyl] - N" - (3 - butyn - 1 - yl)guanidine.

10. N - Cyano - N' - [2 - [(4 - methyl - 5 - imidazolyl)methylthio]ethyl] - N" - (4 - pentyn - 1 - yl)guanidine.

11. N - Cyano - N' - [2 - [(4 - methyl - 5 - imidazolyl)methylthio]ethyl] - N" - (2 - methyl - 3 - butyn - 2 - yl)guanidine.

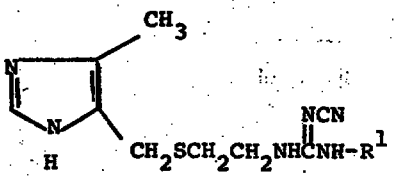
12. N - Cyano - N' - [2 - [(4 - methyl - 5 - imidazolyl)methylthio]ethyl] - N" - (3 - butyn - 2 - yl)guanidine.

13. N - Cyano - N' - [2 - [(4 - methyl - 5 - imidazolyl)methylthio]ethyl] - N" - propargyl - guanidine.

14. A non-toxic pharmaceutically acceptable acid addition salt of a compound as claimed in any one of the preceding claims.

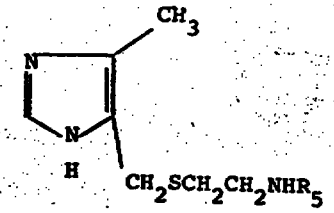
15. A non-toxic pharmaceutically acceptable acid addition salt as claimed in claim 14 which is a salt with hydrochloric, hydrobomic, sulfuric, sulfamic, phosphoric, nitric, maleic, fumaric, succinic, oxalic, benzoic, methanesulfonic, 1,2-ethanedisulfonic, benzenesulfonic, acetic, propionic, tartaric, citric or d-camphorsulfonic acid.

16. A process for the preparation of a compound of the formula:



I

wherein R^1 is a straight or branched chain alkynyl group containing from 3 to 9 carbon atoms, inclusive, or a non-toxic pharmaceutically acceptable acid addition salt thereof which process comprises reacting in a non-reactive solvent at a temperature above ambient temperature a compound of the formula

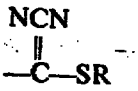


II

or an acid addition salt thereof with a compound of the formula

$$R_6NHR^1 \qquad \text{III}$$

wherein R^1 is as defined above and one of R_5 and R_6 is H and the other is the group

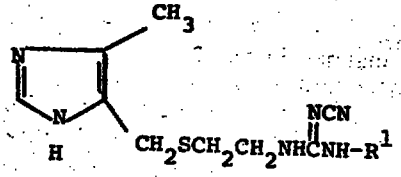


where —SR is a leaving group, and, if desired, converting the resulting compound of formula I basic form or an acid addition salt thereof to the corresponding non-toxic pharmaceutically acceptable acid addition salt or free base form.

17. A process as claimed in claim 16 wherein equimolar quantities of the compounds of formulae II and III are used.

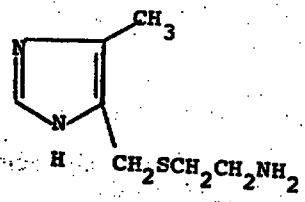
18. A process as claimed in claim 11 or claim 12 wherein R is a (lower)alkyl, aryl, substituted aryl, aralkyl, —CH_2CN, or —CH_2COOR'' group wherein R'' is hydrogen or a C_{1-8} alkyl group.

19. A process for the preparation of a compound having the formula



I

wherein R^1 is a straight or branched chain alkynyl group containing from 3 to 9 carbon atoms, inclusive, or a non-toxic pharmaceutically acceptable acid addition salt thereof which comprises reacting a compound of the formula

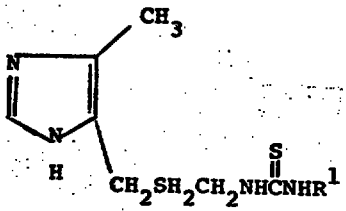


V

with a compound of the formula

$$S{=}C{=}NR^1$$

wherein R^1 is as defined above, to produce the compound

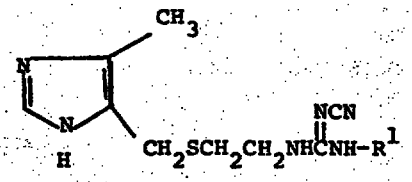


VI

which is then reacted with methyl iodide and cyanamide to produce compound I in basic form and, if desired, converting the product to the corresponding non-toxic pharmaceutically acceptable acid addition salt.

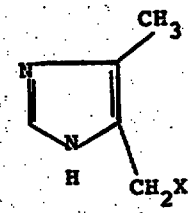
20. A process for the preparation of a compound of the formula

* C L M S *



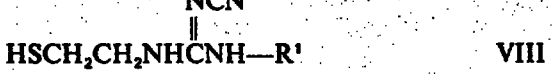
I

wherein R^1 is a straight or branched chain alkynyl group containing from 3 to 9 carbon atoms, inclusive, or a non-toxic pharmaceutically acceptable acid addition salt thereof which comprises reacting in an inert organic solvent a compound of the formula



VII

or an acid addition salt thereof in which X is hydroxy or a leaving group with a compound of the formula



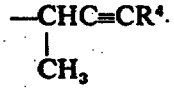
VIII

wherein R^1 is as defined above and, if desired, converting the resulting compound of formula I in basic form or an acid addition salt thereof to the corresponding non-toxic pharmaceutically acceptable acid addition salt or free base form.

21. A process as claimed in claim 20 wherein X is fluoro, chloro, bromo, iodo, $—O_3SR^2$ wherein R^2 is (lower)alkyl, $—O_3SR^3$ wherein R^3 is aryl or substituted aryl, $—O_3SF$, acetoxy or 2,4-dinitrophenoxy.

22. A process as claimed in claim 20 or claim 21 wherein equimolar quantities of the compounds of formulae VII and VIII are reacted in the presence of a base.

23. A process as claimed in any one of claims 16 to 22 wherein R^1 is:



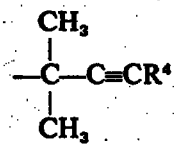
wherein R^4 is H or CH_3.

24. A process as claimed in any one of claims 16 to 22 wherein R^1 is

$$—(CH_2)_nC{\equiv}CR^4$$

wherein R^4 is H or CH_3 and *n* is an integer of from 1 to 6.

25. A process as claimed in any one of claims 16 to 22 wherein R^1 is



wherein R^4 is H or CH_3.

26. A process as claimed in any one of claims 16 to 22 wherein R^4 is H.

27. A process as claimed in any one of claims 16 to 22 wherein R^4 is CH_3.

28. A process as claimed in claim 16, claim 19 or claim 20 substantially as hereinbefore described with reference to the Examples.

29. A compound as claimed in claim 1 whenever prepared by a process as claimed in any one of claims 16 to 28.

30. A pharmaceutical composition for inhibiting gastric acid secretion comprising a compound as claimed in any one of claims 1 to 15, or claim 29 together with a pharmaceutically acceptable carrier or diluent.

* C L M S *

31. A composition as claimed in claim 30 which is adapted for oral administration.

32. A composition as claimed in claim 30 which is adapted for parental administration.

BOULT, WADE & TENNANT,
Chartered Patent Agents,
34 Cursitor Street,
London, EC4A 1PQ

Printed for Her Majesty's Stationery Office, by the Courier Press, Leamington Spa, 1981
Published by The Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.

* C L M S *